DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 4, 2009 has been entered.

The Examiner acknowledges the applicant's remarks and arguments of November 4, 2009 made to the office action filed May 8, 2009. Claims 9, 13, 15, 19-24 and 31-33 are pending. Claim 1 is cancelled and claims 9, 13 and 19-24 are amended. Claims 31-33 are new.

The Declaration filed November 4, 2009 was not considered because it does not pertain to the current application. Particularly, the Declaration of Anil Gulati is directed toward the application no. 10/301,449.

Upon further consideration and for clarification, all previous 35 U.S.C. 103(a) rejections are withdrawn.

Due to previous rejections being withdrawn and the amendments to the claims the new obviousness double patenting rejection and 35 U.S.C. 103(a) rejections are below. Applicant's arguments with respect to claims 1, 9, 15 and 19-24 have been considered but are moot in view of the new ground(s) of rejection.

The claims are examined on the Applicant's election of bosentan as the endothelin antagonist, Alzheimer's as the disease, and tacrine as the cholinesterase inhibitor, as elected on March 20, 2007.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 9, 13, 15 and 19-24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 13-15 and 19-24 of copending Application No. 12/651,647 ('647) in view of Shigeno et al. (Neurosurgery, July 1995, vol. 37, issue 1, pp. 87-91).

This is a provisional obviousness-type double patenting rejection.

Application '647 teach a method of treating Alzheimer's disease comprising administering a mammal a effective amount of a specific endothelin-A antagonist (see claim 1) that can be administered with a cholinesterase inhibitor such as tacrine (see claims 13-15). The administration can be simultaneously, in a single composition, or from separate compositions (see claims 19-24).

Application '647 does not teach bosentan.

Shigeno et al. teach that bosentan is a potent enothelin-1 (ET1) receptor antagonist *in vivo* via injection (addresses claim 31; see abstract). ET1 receptors acts on both ETA and ETB receptors (see abstract).

To one of ordinary skill in the art at the time of the invention would have found it obvious to combine the method of '647 and bosentan because Shigeno et al. teach that bosentan is a potent enothelin-1 (ET1) receptor antagonist *in vivo* via injection (addresses claim 31; see abstract). Further, ET1 receptors acts on both ETA and ETB receptors.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(1) Claims 9 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aliev et al. (Brain Pathology; Jan 2002, vol. 12, pp. 21-35) in view of Shigeno et al. (Neurosurgery, July 1995, vol. 37, issue 1, pp. 87-91).

Aliev et al. teach that blocking ET-1 receptor activity with a specific antagonist has been proposed as a treatment for various vascular and non-vascular diseases such as Alzheimer's Disease. High levels of ET-1 induces the endothelial cell stress reaction

and contribute to the chronic contraction, denudation and desquamation of endothelial cells in Alzheimer's disease (see page 29, left column, paragraph three in its entirety). Further, ET-1 receptor antagonists and pro-antiogenic stimuli will have a beneficial influence in Alzheimer's patients (see page 29, last paragraph, lines 1-5).

Aliev et al. does not teach bosentan.

Shigeno et al. teach that bosentan is a potent enothelin-1 (ET1) receptor antagonist *in vivo* via injection (addresses claim 31; see abstract).

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious and motivated to provide bosentan of Shigeno et al. in the treatment of Alzheimer's as taught by Aliev et al. parenterally, because of the following teachings: 1) Aliev et al. teach that ET-1 receptor antagonists will have a beneficial influence in Alzheimer's patients (see page 29, last paragraph, lines 1-5); and 2) Shigeno et al. teach that bosentan is a potent enothelin-1 (ET1) receptor antagonist *in vivo* via injection (i.e. parenterally; see abstract). Thus, one of ordinary skill in the art would have been motivated to provide the bosentan in the method of Aliev et al. with the expectation of providing a compound capable of treating Alzheimer's disease.

(2) Claims 13, 15, 19-24, 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aliev et al. (Brain Pathology; Jan 2002, vol. 12, pp. 21-35) in view of Shigeno et al. (Neurosurgery, July 1995, vol. 37, issue 1, pp. 87-91). as applied to claim 9 above in further view of Woolf (US 5,466,696) and Meade et al. (US 2002/0183347 A1).

The teachings of Aliev et al. and Shigeno et al. are as applied to claim 9 above.

Aliev et al. and Shigeno et al. do not teach a cholinesterase inhibitor, particularly the Applicant's elected compound tacrine as disclosed in claims 13 and 15. Aliev et al. and Shigeno et al. also do not teach treatment regime disclosed in claims 19-24, nor the amounts of bosentan (claim 32) as a tablet, capsule or powder (claim 33).

Woolf teaches tacrine and cytochrome P450 oxidase inhibitors and methods of use (see title). Clinical studies have been performed on patient's suffering from Alzheimer's disease by utilizing tacrine (see column 1, lines 26-27).

Meade et al. teach composition comprising anticholinergics and endothelin antagonist such as bosentan (see abstract and claim 11) for oral or parenteral administration such as an inhalable powder (see paragraph 10).

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious and motivated to provide the tacrine of Woolf in the Alzheimer's a treatment method of Aliev et al. and Shigeno et al., because both Aliev et al. and Woolf teach treatments of Alzheimer's disease. Therefore, it is considered that one of ordinary skill in the art would have been motivated to provide tacrine in the Alzheimer's treatment method of Aliev et al. and Shigeno et al., with the expectation of providing a compound capable of treatment of the condition. Note it is considered that "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980.)

Regarding claims 19-24 and 32, Aliev et al., Shigeno et al. and Woolf render obvious providing a combination therapy of the endothelin antagonist bosentan and the ACE inhibitor tacrine for the treatment of Alzheimer's disease. Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the treatment regime, such as by providing the therapeutic agents in the same or separate compositions, or by administering one of the compounds prior to the other, according to the guidance provided by Hughes et al. in view of Wu in further view of Woolf, to provide the desired Alzheimer's treatment. It is noted that "[W]here the general conditions of a claim are

disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.) It is furthermore noted that, regarding the order of administration as recited in claims 23-24, it has been held that merely changing the order of steps in a multi-step process is not a patentable modification absent a showing of unexpected results. *Ex parte Rubin* 128 USPQ 440 (POBA 1959.)

Regarding claim 33, Aliev et al., Shigeno et al. and Woolf render obvious providing a combination therapy of the endothelin antagonist bosentan and the ACE inhibitor tacrine for the treatment of Alzheimer's disease. Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to administer bosentan orally as a powder because bosentan can be administered as a powder through an inhaler as taught by Meade et al. (see paragraph 10 and claim 11).

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 9:00 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kendra D Carter/
Examiner, Art Unit 1627

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627